Amendments to the Specification:

Please amend the specification as indicated below.

Please replace paragraph [0034] of the application (paragraph [0032] of pre-grant publication 20060106100) with the following amended paragraph:

[0034] In a specific embodiment of the invention, the obtained cyclopalladated compounds are represented in the Schemes 3 and 4 below, respectively derived from N,N-dimethyl-benzylamine (scheme 3) and from ~~alkines~~ alkynes pyridinyl-phenyl-~~ethine~~ ethyne (scheme 4A) and 1-phenyl-3-N,N-dimethylamine-~~propine~~ propyne (scheme 4B).

Please replace paragraph [0071] of the application (paragraph [0064] of pre-grant publication 20060106100) with the following amended paragraph:

[0071] FIG. 16 presents the in vivo antitumor activity of compounds analogue to drug 1, now containing functionalized ~~alkines~~ alkenes derived from functionalized alkynes as cyclometalling agent.

Please replace paragraph [00130] of the application (paragraph [0115] of pre-grant publication 20060106100) with the following amended paragraph:

[00130] The intensities of fluorescence signals were monitored by a thermostatic spectrofluorimetry Hitachi F-2000. Wavelength was calibrated at 380 nm for

excitation and 440 nm for emission. The activation of the enzyme was made by incubation for five minutes at 37°C in a buffer solution of 50 mM sodium phosphate (pH 6.4) containing NaCl 200 mM, EDTA 1 mM and DTT 2 mM. Measurements were taken in the same activation buffer of cathepsin B and kynetic standards were set up by taking the initial ~~hydrolisis~~ hydrolysis rate under various concentrations of the substrate in the presence or absence of different concentrations of organometal compounds. The results were analysed by non-linear regression by using the software GraFit 3.01 (Erithacus Software Ltd.).

Please replace paragraph [00131] of the application (paragraph [0116] of pre-grant publication 20060106100) with the following amended paragraph:

[00131] The kynetic model of Scheme 1 describes the effect of heparin over the ~~hydrolisis~~ hydrolysis of Z-Phe-Arg-MCA by cathepsin B:

Please replace paragraph [00134] of the application (paragraph [0118] of pre-grant publication 20060106100) with the following amended paragraph:

[0134] Kynetic studies were made for the cyclopalladated complex [Pd (C^2,N-(R+dmpa)(dppf)N_3]. As shown by the FIG. 1A, the presence of organometal in the kynetic test of Cathepsin B results in a reduction of the values k_{cat} for the ~~hydrolisis~~ hydrolysis of Z-*Phe-Arg*-MCA. On the other hand, Figure 1B shows that the compound also notedly increases the affinity of Cathepsin B by the substrate Z-*Phe-Arg*-MCA. The effect of organometal over the activity of endopeptidase Cathepsin B can be described by means of a mixed hyperbolic curve with inhibition standard as

shown by Scheme 1. The efficiency of the substrate ~~hydrolisis~~ hydrolysis system can be changed by modifications in K_S (parameter α) or V_{max} (parameter β). Data were treated according to Equation 1, by using non-linear regression and the values for the constants were calculated. Results show that [Pd (C^2,N-(R+dmpa)(dppf)]N^3 is linked to free Cathepsin B (E) with dissociation constant K_H = 12 ± 1 μM and the compound is linked to the enzyme-substrate (ES) complex with dissociation constant αK_H = 2.4 ± 0.3 μM. The complex also induced a 5.3-time increase of the affinity between Cathepsin B and the substrate Z-Phe-Arg-MCA; Ks value was reduced from 110 ± 15 to 21 ± 2 μM in the presence of the organometal compound, α = 0.19 ± 0.02 (Fig. 1B), while the value of k_{cat} in the presence of [Pd(C^2,N-(R+dmpa)(dppf)]N_3 was also reduced 5.6 times, β = 0.18. ± 0.02. The cyclopalladated compound reduced the product formation constant to 36 (β = 0.18 ± 0.02) in the same proportion increasing the affinity of Cathepsin B by the substrate Z-Phe-Arg-MCA (α = 0.19 ± 0.02), i.e., .α = β. Despite Cathepsin B having been strongly inhibited by the organometal complex (81% inhibition), its efficiency for that substrate in the presence of the organometal complex was not changed, β/α =1.1 ± 0.1. The ~~hydrolisis~~ hydrolysis rate of the second order substrates was the same, k_{cat}/Ks=4.5 10^5 $M^{-1}s^{-1}$, in the presence or absence of [Pd (C^2,N-(R+dmpa)(dppf)]N_3.

Please replace paragraph [00135] of the application (paragraph [0119] of pre-grant publication 20060106100) with the following amended paragraph:

[00135] Cathepsin B and other cysteine-proteases pertaining to the papain superfamily contain highly conserved folding structure (Turk, V.; Bode, W., *Lysosomal cysteine proteinases and their inhibitors cystatins. Innovations in Proteases and their Inhibitors.* Aviles, F. X. (Ed.), Walter de Gruyter & Co., Berlin,

Germany, 1993). These enzymes are linked to peptide substrates and use the pair of ions thiolate-imidazolium to act in its proteolytic activity. This association between the cysteine residue and histidine grants high nucleofilicity to the active site of the cysteine (Michaud, S.; Gour, B. J., *Cathepsin B inhibitors as potential anti-metastatic agents*. Exp. Opin. Patents., 1998, 8, 645-672). The rupture of amide linkages of the substrate involves the formation of an intermediate acyl enzyme. After the formation of the non-covalent complex of Michaelis, the active site thiolate attacks the peptide linkage to form an oxianion which is stabilized in the so-called "oxianion channel" by a glutamine residue. The collapse of the tetrahedric intermediate results in the acyl enzyme and releases product. Subsequently, the ~~hydrolisis~~ hydrolysis of the acyl enzyme regenerates the catalytic ionic pair and releases the new product, i.e. carboxylic acid. Example 5 shows enzymatic inhibition assays by means of the compounds of the invention.

Please replace paragraph [00187] of the application (paragraph [0171] of pre-grant publication 20060106100) with the following amended paragraph:

[00187] The compounds of the invention can also be coupled to soluble polymers as possible drug carriers. These polymers can include ~~polyvinylpirrolidone~~ polyvinylpyrrolidone, ~~piran~~ pyran copolymer, ~~poly-hydroxypropylmethacrilamidephenol~~ poly-hydroxypropylmethacrylamidephenol, poly-hydroxyethylaspartamidephenol or polyethylene ~~oxide-polylisine~~ oxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the invention can be coupled to a class of useful biodegradable polymers to reach the controlled release of a drug, such as polylactic acid, polyglucolic acid, copolymers of polylactic and polyglucolic acid, polyepsilon caprolactone, poly-hydroxy butyric acid,

polyorthoesters, polyacetals, ~~polydi-hydropirans~~ polydi-hydropyrans, ~~polycianoacilates~~ polycyanoacylates and crosslinked or amphypathic block copolymers of hydrogels.

Please replace paragraph [00319] of the application (paragraph [0289] of pre-grant publication 20060106100) with the following amended paragraph:

[00319] *In vitro* assays were made to verify the cytotoxic effect of cyclopalladated compounds of murine melanoma B16F10-Nex2 cells. The cells were incubated for 24 hours under different concentrations. Cell viability was determined by an assay with MTT. As shown in FIG. 13, 100% efficiency is observed under concentration about 1.25 μM of the drugs containing ethane biphosphine (drugs 1, 2 and 3). The same efficiency is noted in the drug containing bis-diphenylphosphine-ferrocene, but under higher concentration, 10 μM (drug 6) and for cyclopalladated compounds containing functionalized ~~alkines~~ alkenes derived from functionalized alkynes (drug 10), about 20 μM. Figure 13 shows the described cytotoxic effect, in which the reduction percentuals of cell viability, in comparison to a control with cells with no drugs, are represented over the bars.

Please replace paragraph [00324] of the application (paragraph [0294] of pre-grant publication 20060106100) with the following amended paragraph:

[00324] Drugs with functionalized ~~alkines~~ alkenes derived from functionalized alkynes were also tested *in vitro* (Figure 16) following the same protocol and presented cytotoxic effect of 100%, about 100 μM. This effect is represented in the following figure, also showing that, among them, drugs 11 and 14 presented significant inhibition from 40 to 50%, about 1 μM.

Please replace paragraph [00325] of the application (paragraph [0295] of pre-grant publication 20060106100) with the following amended paragraph:

[0295] Result analysis offers some important co-relations between chemical structure and drug activity. 100% efficiency is observed under a concentration of about 1.25 μM of the drugs containing ethane biphosphine (drugs 1, 2 and 3). The same does not occur for cyclopalladated compounds containing functionalized ~~alkines~~ alkenes derived from functionalized alkynes (drug 10), in which a concentration about 20 μM is required. From all tested drugs, we can notice that drugs 1 and 6 were those presenting an inhibitory effect over tumor development of about 60% over other drugs. We can see the drug 1 as being the most efficient one to inhibit tumor development, but test animals treated with drug 6 present a lower number of deaths. From the complexes containing functionalized ~~alkines~~ alkenes, drugs 11 and 14 are those presenting significant inhibition, from 40 to 50%, of about 1 μM.